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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/945,805 | 01/06/98 | MORISHITA R | 0018-0993-0P |

HM12/0623
OBLON SPIVAK MCCLELLAND MAIER & NEUSTADT
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON VA 22202

| EXAMINER | |
|---|---|
| MCGARRY,S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | 7 |

**DATE MAILED:** 06/23/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

file

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 08/945,805 | Morishita et al |
| **Examiner** | **Group Art Unit** |
| Sean McGarry | 1635 |

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-23* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is drawn to a pharmaceutical composition that comprises an NF-κB decoy which is defined in the specification to be "any compound that specifically antagonizes the NF-κB binding site. . ." The instant specification discloses one NF-κB decoy. This decoy is a double stranded oligonucleotide SEQ ID NO: 1.

One of skill in the art would not immediately envision the structure of any other NF-κB decoy based on the structure of the exemplified SEQ ID NO: 1. The disclosure of SEQ ID NO: 1 does not convey that applicant has possession of the claimed invention at the time of filing.

2. Claims 7, 9, and 17-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites the limitation "the NF-κB decoy". There is insufficient antecedent basis for this limitation in the claim.

Claim 7 recites "or variants thereof". This language is vague and indefinite. The instant specification provides no definition of what a "variant" might be thus rendering the claim vague and indefinite.

Claims 17-23 provide for the use of an NF-κB decoy, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

3. Claims 17-23 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

4. Claims 1-6, and 8-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of NF-κB via the NF-κB decoy defined as the double stranded nucleic acid SEQ ID NO: 1, does not reasonably provide enablement for the broad range of NF-κB decoys or for treating or preventing the broad range of diseases instantly claimed. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The instant specification discloses one NF-κB decoy defined as a double stranded oligonucleotide SEQ ID NO: 1. The instant specification fails to provide sufficient guidance for one of skill in the art to make and use other NF-κB decoys. Example 3 of the instant specification discloses the reduction of mechanically induced infarction in rat heart via the local administration of SEQ ID NO: 1. Example 4 discloses the inhibition of liver tumor nodules in mouse liver after treating mice with SEQ ID NO: 1 after intravenous injection of murine reticulum cell carcinoma cells. Example 5 discloses the reduction of subdermally transplanted murine colon cancer in mice after the local administration of SEQ ID NO: 1.

The art of nucleic acid based therapy is an unpredictable art. Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the

same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379). The claimed invention is drawn to nucleic acid therapy. A recent review by Stull et al discloses the many problems faced by artisans in the application of these systems *in vivo* and in cell culture. Stull discloses (page 476, left column second full paragraph) "[n]ucleic acid drugs must overcome several formidable obstacles before they can be widely applied as therapeutics. These obstacles require improving the stability of polynucleotide drugs in biological systems, optimizing the affinity and efficacy of the drug without reducing its selectivity, and targeting delivering nucleic acids across cell membranes." Stull et al further disclose(page 476 last paragraph bridging to page 477) " . . . none of the modalities proposed to date can eliminate the disease/target. Thus suppression of disease will require the continued presence of the agent until the disease is cured or the condition is eliminated . . . This makes treatment of chronic disorders such as HIV infection a difficult undertaking. An obvious solution to the persistence issue for agents that are composed of RNA is to have the patient produce their own medicine via the gene therapy route. This approach reduces the requirement for frequent administration but does not circumvent the other two issues, access and entry into the target cell." Stull further discloses in the subsequent paragraph "[i]f the target is outside the vascular system, the agent will have to extravasate. Non-gene nucleic acids drugs have

molecular weights in the 3,000-10,000 Dalton range so extravasation is not a particular problem for the agent itself. However, as these drugs do not permeate into the cytoplasm of cells but are found primarily in the endosome compartment, they will most likely require some covalent modification or delivery system to mediate their efficient entry into the cytoplasm of the target cell. Numerous delivery agents have been developed to facilitate uptake of oligonucleotides in cell culture. These include attempts to modify the ionic backbone, modifications to increase hydrophobicity(e.g., attachment of cholesterol) as well as attempts to attach a targeting ligand such as biotin or a neoglycoprotein directly to the nucleic acid drug. To date these efforts have led to improved uptake but not to improved cytoplasmic delivery." Golden, F. [TIME, May 18, 1998, page 44] discusses the lack of a nexus between mouse models and a cancer therapy. Applicant has provide general guidelines for modes of administration etc. but does not provide any specific guidance such that one of skill in the art could practice the instant invention without undue trial and error experimentation. The instant specification does not teach one of skill in the art any other NF-κB decoy other than SEQ ID NO: 1 and fails to teach one of skill in the art how to predictably formulate any other NF-κB decoy. The instant specification provides model experiments where it is unclear how these artificial models correlate to the treatment or prevention of any specific disease, especially in view of the art cited above.

5. Claims 1-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Russell et al [WO 95/12415].

Russell et al disclose a pharmaceutical composition comprising a nucleic acid sequences that comprises the 8th through 17th nucleotides of SEQ ID NO: 1 of the instant specification (see SEQ ID NO: 1 and claims 1-44 of Russell et al, for example).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

6. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al as applied to claims 1-8 above, and further in view of Stull et al (cited above).

The instant invention is drawn to a pharmaceutical composition that comprises a NF-κB decoy. Russell et al teach a pharmaceutical composition comprising a nucleic acid sequences that comprises the 8th through 17th nucleotides of SEQ ID NO: 1 of the instant specification. Russell et al do not specifically teach a liposomal construct comprising such, however Stull et al teach at Table VI, for example, the use of liposomes and their advantages for the administration of nucleic acids to cells. It would have been obvious for one of ordinary skill in the art to combine the teachings of Russell et al and Stull et al since Russell et al teach the use of a NF-κB nucleic acid decoy and Stull et al have taught the advantages of using liposomes for their administration to

cells. The invention as a whole would therefor have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant filed a new CRF and paper copy of the sequence listing on 5/4/99. On page 13 of the specification these sequences are disclosed. One sequence is a double stranded NF-κB decoy instantly identified as SEQ ID NO: 1 and SEQ ID NO: 3 and a scrambled decoy oligonucleotide instantly identified as SEQ ID NO: 2 and SEQ ID NO: 4. In view of the double stranded nature of these oligonucleotides SEQ ID NO: 3 and 4 are incorrectly represented in the sequence listing. The orientation of these sequences would be 3'-5' in the specification but are conversely oriented in the sequence listing. Applicant **must** correct and satisfy the sequence rules in response to this office action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean McGarry whose telephone number is (703) 305-7028.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. Papers should be faxed to Art Unit 1635 via the PTO Technology Center Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see C.F.R. 1.6(d)). The Art Unit 1635 FAX number is (703) 308-4242 or (703) 305-3014. NOTE: If Applicant **does** submit a paper by Fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Sean McGarry

June 21, 1999

George C. Elliott, Ph.D.
Supervisory Patent Examiner
Technology Center 1600